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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/027,797	BRIGHAM ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,37-41 and 54-57* is/are pending in the application.

4a) Of the above claim(s) *55-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,37-41 and 54* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *6-6-02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of group I, claim 1, in the reply filed on 5-20-04 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 36-53 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 5-20-04.

Applicants' amendment filed 5-20-04 has been entered. Claims 2-36 and 42-53 have been canceled. Claims 1 and 37-41 have been amended. Claims 54-57 have been added. Claims 1, 37-41 and 54-57 are pending.

Since the amendment filed 5-20-04 has amended claims 37-41 to depend on claim 1, therefore, claims 37-41 will be considered as the elected invention. Claims 55-57 are directed to a method for inhibiting production of IL-8 by a respiratory cell in a subject by administering a nucleic acid encoding alpha1 antitrypsin to the subject so as to treat chronic obstructive pulmonary disease in the subject. The subject matter of claims 55-57 is patentably distinct from that of claims 1, 37-41 and 54, which are directed to a method for enhancing delivery of alpha1 antitrypsin to a respiratory cell in a subject by administering a nucleic acid encoding alpha1 antitrypsin to said subject, wherein the blood concentration of alpha1 antitrypsin encoded by the nucleic acid displayed an enhanced alpha1 antitrypsin activity as compared to the same blood level of administered recombinant alpha1 antitrypsin protein. Therefore, claims 55-57 will not be considered by the examiner in the present invention.

Claims 1, 37-41 and 54-57 are pending and claims 1, 37-41 and 54 are under consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim 38 recites the limitation "the positively charged liposome" in line 1. There is insufficient antecedent basis for this limitation in the claim. There is no "positively charged liposome" recited in claim 1.

5. Claim 38 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 38 contains the trademark/trade name Lipofectin™. Where a trademark or trade name is used in a claim as limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112 second paragraph. See Ex Parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claims' scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the trademark/trade name is used to

identify/describe a positively charged liposome, and accordingly, the identification/description is indefinite.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1, 37-41 and 54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for reducing endotoxin induced increase in pulmonary vascular resistance (PVR) by intravenously administering DOTMA/DOPE liposome complexed PCMV4AAT, which expresses alpha1 antitrypsin, into piglets as compared to intravenously administered recombinant alpha1 antitrypsin into piglets, does not reasonably provide enablement for enhancing delivery of alpha1 antitrypsin by administering any vector expressing alpha1 antitrypsin via various administration routes, wherein the blood concentration of alpha1 antitrypsin encoded by the nucleic acid displayed an enhanced alpha1 antitrypsin activity as compared to the same blood level of administered recombinant alpha1 antitrypsin protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 1, 37-41 and 54 are directed to a method for enhancing delivery of alpha1 antitrypsin to a respiratory cell in a subject by administering a nucleic acid encoding alpha1 antitrypsin, such as human alpha1 antitrypsin, to said subject, wherein the blood concentration of alpha1 antitrypsin encoded by the nucleic acid displayed an enhanced alpha1 antitrypsin activity

as compared to the same blood level of administered recombinant alpha1 antitrypsin protein. Claim 37 specifies the nucleic acid encoding alpha1 antitrypsin is associated with a positively charged liposome. Claim 38 specifies the charged liposome is Lipofectin™. Claim 39 specifies the respiratory cell is a nasal mucosal cell or a lung epithelial cell. Claim 54 specifies the subject has chronic obstructive pulmonary disease.

The specification discloses intravenous administration of DOTMA/DOPE liposome complexed PCMV4AAT, which expresses alpha1 antitrypsin, into piglets 48 hours prior to endotoxin administration and intravenous administration of recombinant alpha1 antitrypsin into piglets 1 hour prior to endotoxin administration. The specification shows reduction of endotoxin induced increase in pulmonary vascular resistance (PVR) by intravenously administering DOTMA/DOPE liposome complexed PCMV4AAT, where the alpha1 antitrypsin is distributed throughout the vascular wall and lung parenchyma and the surface of the endothelium, as compared to intravenously administered recombinant alpha1 antitrypsin protein, where the alpha1 antitrypsin is localized to the vascular endothelium only (see specification, p. 27-29). The claims encompass using any vector expressing alpha1 antitrypsin via various administration route for gene delivery and the blood concentration of alpha1 antitrypsin encoded by the nucleic acid displayed an enhanced alpha1 antitrypsin activity as compared to the same blood level of administered recombinant alpha1 antitrypsin protein.

The specification fails to provide adequate guidance and evidence for whether the alpha1 antitrypsin encoded by nucleic acid would have enhanced alpha1 antitrypsin activity than the recombinant alpha1 antitrypsin in vitro or in vivo. The specification also fails to provide adequate guidance and evidence for whether any vector expressing alpha1 antitrypsin delivered

to a subject via various administration route would provide expressed alpha1 antitrypsin that shows enhanced alpha1 antitrypsin activity than a recombinant anlpha1 antitrypsin protein.

The specification only shows reduction of endotoxin induced increase in pulmonary vascular resistance (PVR) when DOTMA/DOPE liposome complexed PCMV4AAT is administered intravenously into piglets. The specification fails to specifically measure and compare the alpha1 antitrypsin activities of nucleic acid encoded antitrypsin and recombinant antitrypsin protein in vitro or in vivo and shows that nucleic acid encoded alpha1 antitrypsin has enhanced antitrypsin activity than recombinant antitrypsin. The specification fails to show that the alpha1 antitrypsin activities of nucleic acid encoded antitrypsin and recombinant antitrypsin protein are indeed different from each other. The reduction of endotoxin induced increase in PVR appears to be due to the more widely distributed nucleic acid encoded alpha1 antitrypsin via intravenously administered liposome complex as compared to intravenously administered recombinant alpha1 antitrypsin protein. There is no evidence of record that shows difference in antitrypsin activities between nucleic acid encoded alpha1 antitrypsin and recombinant antitrypsin, and said difference contributes to the reduction of endotoxin induced increase in PVR. Even if the nucleic acid encoded antitrypsin displays enhanced antitrypsin activity as compared to recombinant antitrypsin, the specification also fails to provide adequate guidance for the correlation between enhanced delivery of alpha1 antitrypsin to a respiratory cell and enhanced antitrypsin activity of nucleic acid encoded antitrypsin. There is no evidence of record that a nucleic acid encoded antitrypsin that shows enhanced antitrypsin activity would result in enhanced delivery of antitrypsin to a respiratory cell in a subject.

Further, the more widely distribution of nucleic acid encoded antitrypsin appears to be due to the longer duration of time between administration of nucleic acid encoding antitrypsin and endotoxin, i.e. 48 hours, as compared to the duration of time between administration of recombinant antitrypsin protein and endotoxin, i.e. 1 hour. The vector used and the administration route affect the efficiency of gene transfer. Deonarain, M. (1998, Expert Opin. Ther. Pat., Vol. 8, pages 53-69) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (Sept. 1997, Nature, Vol. 389, pages 239-242) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression...The use of viruses (viral vectors) is powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells, However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses." (e.g. p. 239, column 3).

In addition, Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself

(volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). In view of the factors that would affect gene delivery as mentioned above, administration route would play an important role in determining the efficiency of gene transfer in vivo.

In view of the reasons set forth above, one skilled in the art at the time of the invention would not know how to enhance delivery of alpha1 antitrypsin to a respiratory cell in a subject by administering any vector expressing alpha1 antitrypsin via various administration routes, such as oral administration, subcutaneous administration and intramuscular administration etc., such that a subject with the blood concentration of alpha1 antitrypsin encoded by the nucleic acid displayed an enhanced alpha1 antitrypsin activity as compared to the same blood level of administered recombinant alpha1 antitrypsin protein.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for this group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER